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Formulation Development and Evaluation of Taste Masked Oral Disintegrating Films of Atenolol by Using Natural Polymers

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ABSTRACT

Fast dissolving/disintegrating films/tablets have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical area. Particularly the fast dissolving drug delivery systems formulated with natural polymers have more demand because natural materials like gums and mucilages have been extensively used in the field of drug delivery for their easy availability, ease administration, non toxicity, non irritant nature etc. Atenolol is β1-selective adrenergic blocking agent and widely used in the treatment of hypertension and angina pectoris. It has a bioavailability of 40-50%. The main objective of the study was to formulate taste masked oral fast disintegrating films of Atenolol to achieve a better dissolution rate by improving the bioavailability of the drug and providing quick onset of action thereby enhancing patient compliance. Oral FDF prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Natural and synthetic superdisintegrants such as croscarmellose sodium (CCS), sodium starch glycolate (SSG) and fenugreek mucilage alone and also in combinations was incorporated to achieve quick onset of action, is to increase the water uptake with in shortest wetting time and there by decrease the disintegration time. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time, folding endurance, percentage of moisture content and *in vitro* dissolution studies and taste mask studies on healthy human volunteers. Among all, the formulation F5 was found to be best formulation which releases 98.89% of the drug within 15 min and disintegration time is 59 sec. which was significantly high when compared to other formulation. The data obtained from *in-vitro* release were fitted into the various kinetic models such as Zero Order, Higuchi, First Order and Korsmeyer–Peppas Model in order to determine the mechanism of drug release. When the regression coefficient values compared, it was observed that 'r' values of formulation F5 was maximum i.e 0.890 hence indicating drug release from formulations was found to follow zero order drug release kinetics.

Keywords: Hypertension, Atenolol, Fast disintegrating films, Solvent casting method, Superdisintegrants, Fenugreek mucilage

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INTRODUCTION

Presently, there is a high level of interest in the use of the oral cavity as a portal for drug entry to the systemic circulation. As a site for drug delivery, the oral cavity offers advantages over the conventional GIT, parenteral and alternative routes of drug administration. Oral thin films are postage stamp-sized rectangular shape polymeric films which instantaneously disintegrate and dissolve within seconds when placed on the tongue. Oral films are preferred by patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders since they are unable to swallow large amounts of water. The advantages of convenient dosing and portability of oral strips have led to a wide applicability of this dosage form in pediatric as well as geriatric patients. The advantages of sublingual delivery of drugs via oral films include larger surface area, enhanced safety, high precision during dose administration compared to liquid forms, high levels of patient compliance, and quicker relief [1]. Additionally, other oral formulations can be subject to poor absorption, or delayed onset due to degradation by the gastrointestinal tract, as well as first pass metabolism by the liver. Also, although oral disintegrating tablets disintegrate quickly, their disintegrated materials remain insoluble until swallowing. Buccal or sublingual delivery through thin films therefore provides a way to circumvent swallowing through rapid dissolution in the oral cavity, thereby causing quick onsets of action at a lower dosage. As the oral film releases the drug instantly, this dosage form can be formulated for to treat diseases, such as pain, allergies, sleep disturbances, anxiety and gastric problems, which require a fast onset of action[2]. Chemically

Atenolol is 4-(2-Hydroxy-3-[(1-methyl ethyl) amino] propoxy) benzene acetamide[3] β_1-blocker is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias and myocardial infarction. The drug is also frequently indicated in the prophylactic treatment of migraine[4]. Administration of conventional tablets of Atenolol has been reported to exhibit fluctuation in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site[5]. Oral bioavailability of Atenolol is around 50% and having half life 6 to 7 hrs[6]. For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion, etc). Majority of investigations on natural polymers in drug delivery systems are centered on polysaccharides and proteins[7]. Number of natural, synthetic and semi synthetic polymer materials is used in the various drug delivery systems[8], but mucilage of natural origin is more preferred over synthetic and semi synthetic substances because they are comparatively cheap, abundantly available, non-toxic and non-irritating in nature[9]. In this study, natural substances like fenugreek seed mucilage was used as superdisintegrants in the formulation of film.

MATERIALS AND METHODS

Materials

Atenolol was obtained as gift sample from Natco Pharma, Hyderabad, India. HPMC was procured from Qualikems fine chem. Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium, aspartame and SLS was obtained from S.D fine chemicals limited, Mumbai. Fenugreek seeds were obtained from local market of Bhopal. All the chemicals used in this work were of analytical grade.

Formulation Development

Extraction and isolation of fenugreek mucilage

The clean, dry fenugreek seeds were grounded under mild conditions using a laboratory mixer. The grounded seeds were then sieved to remove the germ which possesses the lowest hardness. The remaining part was soaked overnight in water, to allow the gum to swell. The swelled gum was separated from the other components of the seeds via filtration through a muslin cloth. The separated gum was either used as it is, *i.e.* in the viscous form or precipitated using commercial ethyl alcohol, dried and finally grinded to fine powder [10].

Formulation development of oral film of Atenolol

Drug (Atenolol) containing FDF were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of Plasticizer were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm*12 films area and was dried at controlled room temperature (25°-30°C, 45%RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. The compositions of the formulations were shown in table 1.

Table 1 Formulation of Atenolol oral fast disintegrating films

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6
Atenolol	300	300	300	300	300	300
HPMC	250	500	750	250	500	750
PEG-400	150	150	150	150	150	150
SSG	150	200	250	-	-	-
CCS	-	-	-	150	200	250
SLS	10	-	-	10	-	-
Fenugreek mucilage	4	4	4	6	6	6
Citric acid	100	100	100	100	100	100
Aspartame	10	10	10	10	10	10
Glycerin	-	-	-	-	-	-
DM water qs to (ml)	-	-	-	-	-	-

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug? = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 300mg.

Evaluation of mucilage

The separated mucilage was evaluated for swelling index, loss on drying, density, compressibility index and angle of repose.

Determination of swelling index

The swelling index is the volume in ml occupied by 1g of drug; including any adhering mucilage after it has been swollen in an aqueous liquid for 4h .The swelling index of fenugreek mucilage powder, was determined according to the (*Kumar et al* 2014)[11]. One gram of mucilage powder was taken in a 25 ml ground glass stoppered cylinder graduated over a height of 120 to 130 mm in 0.5 divisions. To this 25 ml of water was added and this was shaken vigorously every 10 m for 1h and then allowed to stand for 24 h. The volume occupied by mucilage was measured. The Swelling index was calculated from the mean of three determinations.

Swelling Index % (SI) = (W2 – W1/W1) x 100 ---------- (1)

W1= Initial Volume in ml, W2= Final Volume in ml

Loss on drying

Loss on drying is directly measured by IR moisture balance (Labgo Infrared Moisture Balance). Firstly calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 15 minutes and constant reading set the knob and check % moisture.

Evaluation of prepared Film[12-15]

The formulations were evaluated by the following tests.

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 282nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (4.15cm2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Atenolol was determined using UV-Visible spectrophotometer at 282nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

RESULTS AND DISCUSSION

The percentage yield of mucilage was found 46.0%. The loss on drying and swelling index of isolated mucilage was found to be 73.867±1.338% and 162.478±1.022% respectively. λ_{max} of Atenolol was found to be 282 nm in 6.2 pH phosphate buffer solution by using U.V. spectrophotometer (Labindia-3000+). The general appearance, weight variation and thickness of all the films were within acceptable limits table 2.

Table 2 Result of general appearance, thickness and weight variation

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Translucent	88±5	110±2
F2	Translucent	90±4	114±3
F3	Translucent	92±8	115±4
F4	Translucent	95±5	120±2
F5	Translucent	98±4	123±4
F6	Translucent	90±5	125±1

***Average of three determinations (n=3)**

The results for folding endurance, disintegrating time, tensile strength, % of moisture content and % Assay were shown in table 3. Tensile strength value of optimized formulation (F5) was 0.556±0.056kg/cm^2 and percent Assay 99.32±0.32 %. The folding endurance of the optimized oral fast disintegrating formulation (F5) was 168±3. The assay values of all the formulations were ranging from 96.65±0.21 to 99.32±0.32%. The disintegration time was ranging between 50±5 to 120±4 sec. The final formulation shows better drug release (98.89%) compared to other formulation within 15 m (Table 4). The cumulative percentage (%) drug release profile and the assay of the F5 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug. The *in vitro* drug release data of the formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values compared, it was observed that 'r' values of formulation was maximum i.e 0.890 hence indicating drug release from formulations was found to follow zero order drug release kinetics table 5 and fig 1&2.

Table 3 Result of folding endurance, disintegrating time, tensile strength, moisture content & % assay

F. code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength* kg/cm²	% of Moisture content*	% Assay*
F1	125±4	120±4	0.852±0.025	2.95±0.04	98.85±0.23
F2	130±3	89±5	0.785±0.032	2.45±0.05	97.78±0.45
F3	128±4	80±2	0.658±0.014	2.65±0.06	96.65±0.21
F4	135±2	86±4	0.458±0.023	2.32±0.04	98.74±0.28
F5	168±3	59±3	0.556±0.056	1.45±0.02	99.32±0.32
F6	149±4	50±5	0.658±0.074	2.85±0.07	98.58±0.41

***Average of three determinations (n=3)**

Table 4 Results of *In-Vitro* release study of optimized formulation F5

S. No.	Time (Min.)	Cum % Drug release
1.	1	22.36
2.	2	48.89
3.	5	65.58
4.	10	79.98
5.	15	98.89

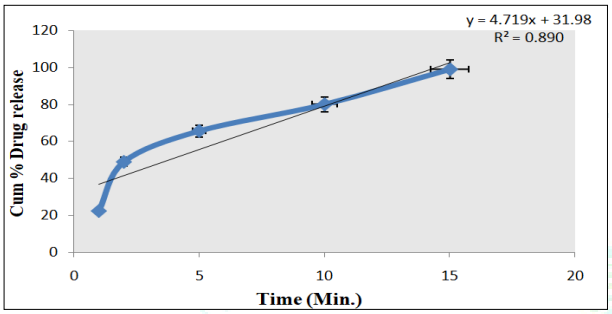

Figure 1 Zero order release kinetics of optimized formulation F5

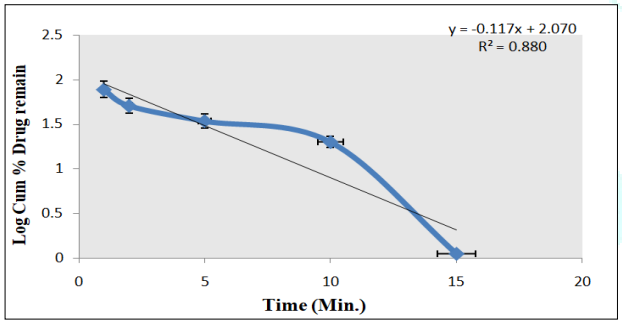

Figure 2 First order release kinetics of optimized formulation F5

Table 5 Kinetics data of Optimized Formulation F5

Formulation	Regression Coefficient	Zero order	First order
F5	r^2	0.890	0.880

CONCLUSION

In the present study the superdisintegrant property of Fenugreek seed mucilage has been explored. Extensive swelling, porosity and wicking action of the natural material in the FDF formulation were found to be contributing its superdisintegrant action. FDF of Atenolol was formulated with an aim to improve the versatility, convenience, patient compliance leading to an enhanced approach for the administration of drug to the pediatrics and geriatrics. Also suitable for clinical use in the treatment of hypertension where a quicker onset of action with the convenience of administration. Further taste masking studies proved that the FDF produced faster onset of action and resulted in complete masking of metallic taste of Atenolol and hence, improved the patient compliance. Based on results, formulation F5 was the best one from prepared FDF formulations. Stability studies were carried out for 3 months and all the formulations were found to be stable after 2 months.

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